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C-Reactive Protein and Interleukin-6 as Diagnostic Biomarkers for Bacterial Sepsis: Protein C-Reaktif dan Interleukin-6 sebagai Biomarker Diagnostik untuk Sepsis Bakteri

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General Background: Sepsis merupakan kondisi berbahaya akibat respon imun yang tidak terkontrol terhadap infeksi bakteri, sehingga diagnosis cepat sangat penting untuk mencegah kematian. Specific Background: Gejala klinis sepsis sering tidak spesifik, sehingga diperlukan biomarker yang dapat membantu deteksi dini. CRP dan IL-6 banyak diteliti karena berperan penting dalam respon fase akut terhadap infeksi. Knowledge Gap: Namun, bukti mengenai akurasi diagnostik dan standar cut-off keduanya masih terbatas dan bervariasi pada populasi berbeda. Aim: Penelitian ini bertujuan mengevaluasi nilai diagnostik CRP dan IL-6 dalam membedakan pasien sepsis bakteri dari individu sehat serta menilai sensitivitas, spesifisitas, dan akurasinya. Results: Studi kasus-kontrol dengan 100 pasien sepsis dan 50 kontrol sehat menunjukkan kadar CRP (65.4 ± 20.3 mg/L) dan IL-6 (72.6 ± 25.7 pg/mL) meningkat signifikan ($p < 0.001$), dengan akurasi diagnostik 89% dan 90%. Novelty: Temuan ini menegaskan potensi CRP dan IL-6 sebagai biomarker yang saling melengkapi dalam deteksi dini sepsis. Implications: Penerapan biomarker ini berpotensi meningkatkan ketepatan diagnosis dan intervensi lebih awal, meski penelitian lanjutan diperlukan untuk standardisasi.

Highlight :

- CRP and IL-6 were significantly elevated in bacterial sepsis patients.
- Both biomarkers showed high sensitivity, specificity, and accuracy.
- Results highlight CRP and IL-6 as reliable early diagnostic markers.

Keywords : Bacterial Sepsis, C-Reactive Protein (CRP), Interleukin-6 (IL-6), Inflammatory Biomarkers, Diagnostic Accuracy

Introduction

Sepsis is a lethal disease of acute dysregulated host response to bacterial infections—characterized by systemic inflammation and, ultimately, cellular damage, multiple organ dysfunction (MOD), and death. Rapid and precise diagnosis of bacterial sepsis is a promising and lifesaving strategy, contributing to improved patient outcomes [1]. However, clinical diagnosis of sepsis is a great challenge, and the symptoms of sepsis are complex and non-specific, which often overlap with those of other inflammatory and infectious diseases. This has raised the need of specific biomarkers for early diagnosis and follow up of bacterial sepsis [2]. Several biomarkers that have been studied, CRP and IL-6 have garnered much attention as they play central roles during the inflammatory burst and both exhibit changes over baseline shortly after infection. C-reactive protein CRP is a hepatic acute-phase reactant synthesized by hepatocytes and secreted into the bloodstream in response to proinflammatory cytokines; particularly IL-6 (3). It is a non-specific but sensitive sign of

tissue injury and inflammation [3]. CRP is the name and one of the acute phase proteins which increases rapidly in the body within 6 to 8 hours of inflammation initiation, and reaches peak levels at 48 hours. It can be used to indicate when an infection or inflammation is occurring [4]. IL-6 is a pleiotropic cytokine that released by many types of cells such as macrophages, T cells, and endothelial cells during the early stage of infection and inflammation [5]. It is an important endogenouse mediator of the acute-phase response, promoting CRP production and directing immune response, including lymphocytes activation and defferenctation. The initial steep rise of IL-6, which often precedes CRP, indicates its potential to be an early diagnostic marker of bacterial sepsis [6]. Research on CRP and IL-6 as diagnostic biomarkers of bacterial sepsis. Elevated CRP concentrations is correlated with the severity of infection and systemic inflammatory response and it, however, in clinical practice it is used as a marker of bacterial infection and sepsis as the most widely used. Consequently, the diagnostic specificity may not be ideal, since CRP elevates in inflammatory states unrelated to infection [7]. By contrast, the fact that IL-6 is an upstream mediator in the inflammatory cascade 9,10 suggests an earlier and potentially more comprehensive insight into sepsis onset and progression. Some studies demonstrated the ability of IL-6 to differentiate bacterial and viral infection and also to predict prognoses of septic patients [8]. The ideal combined biomarker may improve diagnostic performance compared to CRP or IL-6 alone, as the complementary kinetic/cytopathic and biologic roles of CRP and IL-6 allow for a fuller characterization of the inflammatory response. C-reactive protein (CRP) is a marker of active inflammation, and Interleukin-6 (IL-6) is a marker of early immune activation [9]. This hybrid strategy could also help differentiate between bacterial sepsis and other forms of SIRS helps guide antibiotic therapy and assess response to therapy [10]. Despite the promising diagnostic value of CRP and IL-6, challenges remain in establishing standardized cut-off values, understanding their kinetics in diverse patient populations, and integrating these biomarkers into routine clinical protocols. Furthermore, factors such as age, comorbidities, and concomitant medications may influence biomarker levels, complicating interpretation [11][12]. The aim of the study is evaluating the diagnostic value of C-reactive protein (CRP) and interleukin-6 (IL-6) levels in distinguishing patients with bacterial sepsis from healthy individuals, and to assess their sensitivity, specificity, and overall accuracy as reliable biomarkers for early detection

Methodology

This retrospective case-control study was performed between January 1, 2025, and June 1, 2025, in individuals aged 30-45 years. The participants of the study involved 100 patients with the diagnosis of bacterial sepsis and 50 normal controls, which were appointed according to age and sex. Ethical clearance was obtained from the institutional review board and written informed consent was obtained from all participants before recruitment. Subjects were enrolled if they were adult patients (aged 30-45 y) with clinical and microbiological evidence of bacterial sepsis diagnosed by established method. Exclusion criteria were both patients with chronic inflammatory diseases, autoimmune disorders and recent immunosuppressive therapy as well as recent antibiotic treatment before admission. Controls consisted of healthy volunteers with no acute signs of infection or chronic illness. They were matched in age and sex with the cases. Peripheral vein blood was collected from all subjects in a sterile environment. Blood was collected in serum separating gel tubes to separate serum. The tubes were then spin at 3000 rpm for 15 minutes. Blood samples were divided into portions and frozen at −80 °C until analysis for biomarkers. Inflammatory biomarkers, especially C-reactive protein (CRP) expressed in mg/L and Interleukin-6 (IL-6) expressed in pg/mL, were quantified using the Enzyme-Linked Immunosorbent Assay (ELISA) technique. The Bio-Techne (USA) instructions for the ELISA kits and procedures were followed to make sure they were consistent and accurate.

IBM SPSS Statistics version 26 was used to analyze the quantitative data. Frequencies and percentages were used to show descriptive data. Two-tailed independent and paired t-tests were used to compare group means for factors that had a normal distribution. Non-parametric tests, such as the Mann–Whitney U test, Wilcoxon signed-rank test, and Chi-square test, were used when the data were not usually distributed. It was thought that there was statistical significance if the p-

value was less than 0.05.

The study was approved by the Human Ethics Committee of Al-Habboubi Teaching Hospital, Thi-Qar Health Directorate, Iraq, and the College of Education for Girls, Shatrah University. All participants were fully informed about the study's objectives and procedures, and written informed consent was obtained from each participant prior to enrollment. Throughout the entire study, strict protocols were followed to ensure the confidentiality and privacy of all patient data.

Results

A. Sociodemographic Characteristics of Patients with Bacterial Sepsis and Healthy Controls

The table shows the differences in sociodemographic profitability between the 100 patients with bacterial vaginosis and the healthy control group (50 participants). The mean age of the patients was 40.2 ± 3.1 years and 39.8 ± 3.5 years, with no statistically significant differences observed between the two groups (p = 0.35). The table also shows the gender distribution, with 58 males in the visit group compared to 42 females, and 28 males and 22 females in the control group, with no significant difference (p = 0.90). Regarding smoking status, the patients were distributed as follows: 35 smokers and 65 non-smokers, compared to 18 smokers and 32 non-smokers in the control group, with the difference not being statistically significant (p = 0.82). The mean body mass index (BMI) was 27.5 ± 2.8 in patients and 26.8 ± 3.0 in healthy controls, with no significant difference (p = 0.14). Therefore, we achieved consistent gains in both groups, making them a suitable comparison for biological changes (Table 1).

Characteristic	Patients with Bacterial Sepsis (n=100)	Healthy Controls (n=50)	p-value
Age (years), mean ± SD	40.2 ± 3.1	39.8 ± 3.5	0.35
Gender (Male/Female)	58 / 42	28 / 22	0.90
Smoking Status (Yes/No)	35 / 65	18 / 32	0.82
BMI (kg/m²), mean ± SD	27.5 ± 2.8	26.8 ± 3.0	0.14

Table 1. *Comparison of Age, Gender, Smoking Status, and BMI between Study Groups*

Comparisons between groups were performed using the independent samples t-test for continuous variables (age and BMI) and the Chi-square test for categorical variables (gender and smoking status). A p-value < 0.05 was considered statistically significant.

B. Serum C-Reactive Protein (CRP) Levels in Patients with Bacterial Sepsis and Healthy Controls

In the table below, the contrast of serum C-reactive protein (CRP) concentrations in patients with bacterial sepsis and normal, healthy individuals is presented. The average CRP concentration of patients with sepsis is 65.4 mg/L and 20.3 mg/L, SD, higher than that of the control group (4.8 mg/L 2.1 mg/ L, SD). This difference was very statistically significant (p < 0.001), demonstrating the significance and sensitivity of CRP as a biomarker of inflammation and bacterial infection (Table 2).

Group	Mean CRP (mg/L)	Standard Deviation (SD)	p-value vs Controls
Bacterial Sepsis	65.4	20.3	< 0.001
Healthy Controls	4.8	2.1	

Table 2. *Comparison of Mean CRP Concentrations Between Study Groups*

The independent samples t-test was used to compare mean CRP levels between patients and controls. A p-value less than 0.05 indicated statistically significant differences.

C. Serum Interleukin-6 (IL-6) Levels in Patients with Bacterial Sepsis and Healthy Controls

Table Comparison of serum IL-6 concentrations between patients with bacterial sepsis and controls. The mean:A08 level in the patient group was high, 72.6 pg/ml (s 25.7); the control group had low IL-6 levels with a mean of 5.2 pg/ml (s 1.8). The two groups differed significantly from each other ($p < 0.001$), which supported the status of IL-6 as a useful biomarker for the identification of patients with the inflammatory diseases related to a bacterial infection (Table 3).

Group	Mean IL-6 (pg/mL)	Standard Deviation (SD)	p-value vs Controls
Bacterial Sepsis	72.6	25.7	< 0.001
Healthy Controls	5.2	1.8	

Table 3. *Comparison of Mean IL-6 Concentrations Between Study Groups*

An independent samples t-test was performed to compare IL-6 levels between patients and controls, with significance set at $p < 0.05$.

D. Diagnostic Performance of CRP and IL-6 Biomarkers for Bacterial Sepsis

Table 1 Diagnostic performance of CRP and IL-6 as biomarkers for bacterial sepsis expressed in sensitivity (Se), specificity (Sp), PPV, NPV, accuracy, and cut-off values. CRP showed a sensitivity of 88% and specificity of 90%, with a positive predictive value of 94% and a negative predictive value of 80%, and overall accuracy of 89% with a cut-off of 15 mg/L; IL-6 was slightly more sensitive: 92% and specific: 88%, and its positive and negative predictive values and overall accuracy were 92%, 88% and 90% at a cut-off of 10 pg/mL. Such a finding suggests that both of the markers perform well and could be clinically utilized to detect bacteremia at an early stage (Table 4).

Biomarker	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)	Negative Predictive Value (NPV) (%)	Accuracy (%)	Cut-off Value
CRP	88	90	94	80	89	15 mg/L
IL-6	92	88	92	88	90	10 pg/mL

Table 4. *Sensitivity, Specificity, Predictive Values, Accuracy, and Cut-off Levels of CRP and IL-6*

Diagnostic performance metrics were calculated using standard formulas based on true positive, false positive, true negative, and false negative results. Cut-off values were determined by ROC curve analysis to maximize sensitivity and specificity.

Discussion

There were no statistically significant differences in age, sex, smoking, and BMI between patients with bacterial sepsis and healthy controls in the present study. This demographic balance is important to minimize the chance that any differences in biomarkers are due to sex or gender-related confounders, rather than to disease status. Similar results have been observed in other studies comparing baseline characteristics in the presence of near-matching between groups suggesting it is resistant to differences in biomarker comparison [13]. However, some research has

noted that older age and higher BMI are associated with increased risk and severity of sepsis, which could be due to population differences or study design variations [14]. The narrow age range and controlled recruitment criteria in this study likely contributed to the lack of significant demographic variation. Moreover, CRP and IL-6 have proved to be critical inflammatory markers for infection, and markedly elevation of them in bacterial sepsis group than control group is accordingly consistent with that16. The exceptionally high average CRP (65.4 mg/L) also agrees with several reports indicating CRP is sensitive to bacteria and systemic inflammation [15]. Similarly, for IL-6 (72.6pg/mL), this value corresponds to the expectations of it being an early-response cytokine that typically up-regulates rapidly following infective insult [16]. These results are consistent with findings from Liu et al. (2016), who emphasized the diagnostic and prognostic value of these biomarkers in sepsis [17]. Nevertheless, some investigations have suggested IL-6 may provide earlier and more specific indications of infection than CRP, though its rapid fluctuations and short half-life pose challenges in clinical interpretation [18]. The diagnostic performance data further support the utility of CRP and IL-6 as biomarkers for bacterial sepsis, with both markers showing high sensitivity, specificity, and accuracy near 90%. CRP exhibited a sensitivity of 88% and specificity of 90%, while IL-6 showed slightly higher sensitivity (92%) with comparable specificity (88%). These findings are in line with [19], who reported that CRP is a practical and widely used marker in sepsis diagnosis, while IL-6 may offer marginally improved sensitivity. However, the variability reported in literature regarding specificity and predictive values can be explained by the influence of non-infectious inflammation on CRP levels and by differences in timing of IL-6 measurement, which is more time-sensitive [20][21]. Differences in reported biomarker values and diagnostic accuracy across studies are often due to several factors. Timing of sample collection is critical because IL-6 peaks early in the inflammatory cascade and decreases quickly, meaning delayed sampling can underestimate its levels. Chronic inflammatory conditions or comorbidities in some populations can elevate baseline CRP and IL-6, affecting specificity and positive predictive value [22]. Additionally, methodological differences such as assay sensitivity, calibration, and cut-off values contribute to inter-study variability. Genetic and environmental factors influencing cytokine production may also explain population differences in biomarker responses [23].

Conclusion

The study concluded that C-reactive protein (CRP) and interleukin-6 (IL-6) are both highly effective diagnostic biomarkers for bacterial sepsis. The results demonstrated significant elevations of CRP and IL-6 in patients with bacterial sepsis compared to healthy controls, with diagnostic accuracies of 89% for CRP and 90% for IL-6. These findings underscore the potential of CRP and IL-6 as reliable indicators for early detection of sepsis, facilitating timely therapeutic interventions. The study highlights the importance of integrating these biomarkers into clinical practice for more precise and efficient sepsis diagnosis. However, further research is needed to establish standardized cut-off values, assess the role of CRP and IL-6 in diverse patient populations, and explore their combined diagnostic potential alongside other biomarkers.

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